REMARKS

This amendment is responsive to the Final Office Action of December 8, 2008. Reconsideration and allowance of claims 1-18 and 22-29 are requested.

Status of the Claims

Claims 1-18 and 22-30 are pending.

Claims 2-4 and 14 stand withdrawn.

Claims 19-21 were previously cancelled, without prejudice and disclaimer.

Claims 1, 11, 13, 23, and 29 are amended.

New claim 30 is added.

The Office Action

Claims 1, 5-13, 15-18, and 22-29 were rejected under 35 U.S.C. §103(a) as being unpatentable over U.S. Patent No. 7,252,720 to Foster, as modified by *Ernst and Race*, and as further modified by U.S. Application No. 10/467,591 to Kritzler.

The Present Application

Prions are resistant to many conventional treatment processes used for destruction of microorganisms. Their behavior also differs in many cases to that of conventional proteins. In particular, conformational changes in the structure of prions in various treatments results in a β-sheet structure which is highly resistant to degradation.

The present inventors have found that a treatment in which one or more phenols is combined with an inorganic salt, e.g., sodium chloride, can inactivate prions on a body.

The References of Record

The Foster reference discloses a method for removing contamination from ion-exchange chromatography columns. Foster uses sodium chloride solution to elute and remove prions from the column (col. 3, lines 41-44) through a type of ion exchange mechanism (col. 4, lines 31-33). The prions are not destroyed. Specifically, Foster notes that material eluted during the first 2M sodium chloride wash was subsequently found to have high prion infectivity (col. 6, lines 9-30).

The Ernst and Race reference discloses treating a scrapie-infected hamster brain homogenate with LpH. As mentioned in the Ernst and Race article, LpH is an aqueous acid phenolic disinfectant which contains o-benzyl-p-chlorophenol at 6.1%, as well as p-tertiary amylphenol at 3%, and phenylphenol at 0.5%.

Kritzler, et al. discloses methods for treating a surface suspension or solution contaminated with prion protein with enzymes. In paragraph 41, Kritzler discloses that certain surfactants tend to bind to proteins and initiate unfolding of their tertiary structure. In paragraph 42 it is noted that inorganic salts can induce conformational transitions in proteins. These paragraphs detail the understanding about proteins in general and not about prion proteinaceous material. It can be seen from Table 1 that these general assumptions do not apply to prions (as represented by models of proteins such as bovine albumin with high globulin content).

The Claims Distinguish Patentably Over the References of Record

Claim 1 has been amended to recite a method of treating a body which is contaminated with infectious prions. The method includes contacting the body with a composition comprising a phenol and a soluble inorganic salt, to effect a change in the three dimensional structure of the prion protein and inactivate prions on the body.

Support for the amendments to claim 1 are to be found in the specification at page 12, lines 1-5 and page 19, lines 7-14.

The references cited, alone or in combination, do not suggest such a method.

The Examiner cites **Kritzler, et al.** as disclosing that inorganic salts can induce conformational transitions in proteins. As previously noted, these paragraphs of Kritzler detail the understanding about proteins in general and not about prion proteins. The Examiner argues that the Applicant has not provided any reasoning or argument as to why a prion is a unique protein or why the ordinary artisan would expect a different outcome following treatments with detergent than a protein in general.

As noted in the Background of the present specification, the World Health Organization (1997) protocol for prion deactivation calls for soaking the instrument in concentrated sodium hydroxide or hypochlorite for two hours followed by one hour in an autoclave. These aggressive treatments are often incompatible with medical

devices, particularly flexible endoscopes and other devices with plastic, brass, or aluminum parts. Many devices are damaged by exposure to high temperatures. Chemical treatments, such as strong alkali, are damaging to medical device materials or surfaces in general. Glutaraldehyde, formaldehyde, ethylene oxide, liquid hydrogen peroxide, most phenolics, alcohols, and processes such as dry heat, boiling, freezing, UV, ionizing, and microwave radiation have generally been reported to be ineffective. In support of the unique properties of prions, the Examiner's attention is drawn to the following references, all of which are of record in this application:

Antloga, et al. "Prion Disease and Medical Devices", ASAIO Journal, V. 46, N. 6, 2000; pp. S69-S72 XP001092854.

Darbord, "Inactivation of Prions in Daily Medical Practice", Biomedicine & Pharmacotherapy, V. 54, 1999 pp. 34-38 XP002228686.

Rutala, et al., "Creutzfeld-Jakob Disease: Recommendations for Disinfection and Sterilization", Clinical Infectious Diseases, V. 32, N. 9, May 2001 pp. 1348-1356 XP008012867.

Antloga lists in Table 2, on p. S70, several methods which had been shown in the literature to be ineffective against prions. Antloga notes that prion are notoriously very hardy and demonstrate resistance to routine methods of decontamination and sterilization.

In Table II on page 35, Darbord also lists treatments known to be ineffective against treating prions, which includes detergents.

Rutala recognizes that after use, contaminated medical equipment can spread or transmit CJD. Rutala gives the example of electrodes that were implanted in a patient with CJD disease and then cleaned with benzene, followed by sterilization with 70% alcohol and formaldehyde vapor. Two years after this treatment, the electrodes were implanted into a chimpanzee that developed CJD. Thus, this benzene cleaning and alcohol/formaldehyde vapor sterilization technique was ineffective against prions. Rutala goes on to discuss the risk of CJD transmission not only to future patients, but also to healthcare workers who have occasion to handle the prion contaminated medical instruments or devices (page 1350, col. 2).

As set forth further down in column 2, Rutala states: "it has been established that most disinfectants are inadequate for the elimination of prion infectivity". Further, in the first column of page 1353, Rutala notes that "prions exhibit an unusual resistance to conventional chemical and physical decontamination

methods." Rutala goes on to explain that this includes both gaseous and physical processes.

Thus, there is no predictability that a treatment which is effective against proteins in general would have any effect on prions. One of ordinary skill in the art, aware of the wealth of literature on the difficulties or inactivating prions, would have no expectation that a treatment for conventional proteins would also be effective against prions and would treat the non-enabling disclosure of Kritzler as controverted speculation, without any basis in fact.

Further, while most proteins have a hydrophilic character, prions are highly hydrophobic, which would lead one of ordinary skill in the art to expect differences in behavior to conventional proteins.

The **Foster** reference discloses a method for removing contamination from ion-exchange chromatography columns. Foster uses a sodium chloride solution to elute and remove prions from the column (col. 3, lines 41-44) through a type of ion exchange mechanism (col. 4, lines 31-33). The Examiner argues that Foster's ion exchange column constitutes a body. However, Foster does not inactivate prions on the column, he merely removes them.

Foster acknowledges that the salt has no impact on the prions- it is merely used to elute the proteins from the column by an ion-exchange process. The salt is preferentially attracted to the column so the protein is released. The prions released are not inactivated. Specifically, Foster notes that material eluted during the first 2M sodium chloride wash was subsequently found to have high prion infectivity (col. 6, lines 9-30). This also confirms that Kritzler's suggestion that salts can introduce conformational transitions in proteins is not applicable to prions.

Ernst & Race (1993) discloses treating a scrapie-infected hamster brain homogenate with LpH. There is no suggestion in this reference that the composition include a soluble inorganic salt. Ernst & Race purports LpH to be a complete solution to the scrapie infection problem and provides no motivation or reason to incorporate an inorganic salt.

In a subsequent study, (Race and Gregory, Inactivation of Transmissible Spongiform Encephalopathy (Prion) Agents by Environ LpH, J. Virol., pp. 2164-2165, Feb 2004), a copy of which is of record in this application, brain suspensions derived from scrapie-infected hamsters were treated with LpH-SE, a different phenol-based formulation. The results showed a dramatic difference in inactivation between

LpH and LpH-SE, with LpH being 10^4-10^5 times more effective than LpH-SE. This further demonstrates that, as previous authors have noted, prions are extremely difficult to inactivate and their behavior cannot be predicted. There is thus no predictability that Foster's salt would have any influence on Ernst and Race's LpH studies.

In sum, the references alone or in combination, do not suggest a method for the treatment of a body which is contaminated with prions, which includes contacting a body with a composition comprising a phenol and a soluble inorganic salt, such as sodium chloride, to effect a change in the three dimensional structure of the prion protein and inactivate prions on the body. The Examiner argues that there would have been "a reasonable expectation of success given the taught success of each of the applied references in inactivating prion proteins." However, as noted above, the prions are not destroyed by Foster's salt, but retain high reactivity. Thus, there would have been no expectation that combining the Foster, Race and Kritzler references would lead to success. Nor is there any expectation that Foster's salt could, in combination with phenol, effect a conformational change on prion protein, since the prions treated with Foster's salt retained high reactivity, suggesting no conformational change.

The present inventors have found that an inorganic salt, used in combination with one or more phenols, improves the effectiveness of the phenol, especially at low pH. This is believed to be due, at least in part, to the effects on the phenol solubility. This is not taught or suggested by the references.

Accordingly, it is submitted that claim 1, and claims 5-9, 15-16, 18, 22, and 25-28 dependent therefrom, are patentable over the cited references.

Claim 11 calls for a method of treating a medical device which is contaminated with infective prions which includes contacting the device with a composition comprising a non-halogenated phenol and a soluble inorganic salt to inactivate prions on the device, the soluble inorganic salt including sodium chloride.

Support for the amendments to claim 11 are to be found in the specification at page 7, lines 9-10 and page 10, line 32-37, and page 19, lines 7-14.

The references of record do not suggest such a method. The salt treatment method taught by Foster does not destroy prions. Ernst and Race make no suggestion that a non-halogenated phenol would be improved by addition of sodium chloride. The LpH formulation includes o-benzyl-p-chlorophenol, a halogenated phenol. As

shown by the Race and Raymond article LpH-SE, whieh has no halogenated phenol is shown to be much less effeetive. Foster teaehes that salt has no effect on the infectivity of prions. Further, while Foster suggests that the method may be used for cleaning substrates, sueh as surgical instrumcnts, there is no suggestion that the salt solution would inactivate prions on the instruments. Further, Foster has provided no cnabling disclosure of treating such instruments nor provided any reasoning as to why a solution formulated for eluting prions from an ion exchangc column would have any effect on surgical instruments, which are not composed of ion exchange mcdia.

Thus, the prior art provides no motivation for combining a non-halogenated phenol with sodium ehloride. Accordingly, it is submitted that claim 11, and claims 12 and 17 dependent therefrom, are patentable over the eited referenees.

Claim 13 calls for a method of treating a body which is contaminated with infective prions. The method ineludes contacting the body with a composition comprising a phenol to inaetivate prions on the body. The phenol includes *o*-phenylphenol and *o*-benzyl-*p*-ehlorophenol in a solution that includes brine.

The referenees do not suggest sueh a method. None of the references, with the exception of Ernst and Race, suggests treatment with phenol that includes *o*-phenylphenol and *o*-benzyl-*p*-chlorophenol. There is no suggestion in Ernst and Race that such phenols be used in combination with brine. Foster teaches that salt does not destroy infectivity. Kritzler does not suggest that prions undergo conformational ehanges in the presence of brine nor suggest that sueh a eonformational change, if it were to oeeur, would have on prion infectivity. Kritzler indicates that inorganic salts have an effect on conformational changes in eonventional protcins. As Foster demonstrates, this is not generalizable to prions, since the salt treatment of Foster was found to have no effeet on infectivity. Thus, one of ordinary skill in the art would not expect brine to have any effeet on the ability of a combination of *o*-phenylphenol and *o*-benzyl-*p*-ehlorophenol to inactivate infective prions.

Accordingly, it is submitted that claim 13 distinguishes patentably over the references of reeord.

Claim 23 calls for a method of treating a body which is eontaminated with prions that ineludes contacting the body with a composition comprising at least one phenol, the composition eomprising a phenol eoncentration of at least 0.005M and an inorganic salt which is present at a concentration of at least 2% by weight, the phenol including at lcast one of the group eonsisting of *p*-ehloro-*m*-xylenol; thymol;

triclosan; 4-chloro, 3-methylphenol; pentachlorophenol; hexachlorophene; 2,2-methyl-bis(4-chlorophenol); *p*-phenylphenol; 2,3-dimethylphenol; 3,5-dimethoxyphenol; 2,6-dimethoxyphenol; *o*-phenylphenol; *p*-tertiary-amylphenol; *o*-benzyl-*p*-chlorophenol; *p*-chloro, *m*-cresol; *o*-cresol; p-cresol; 2,2-methylenebis(*p*-chlorophenol); 3,4-dihydroxybenzoic acid; *p*-hydroxybenzoic acid; caffeic acid; protocatechuic acid; *p*-nitrophenol; 3-phenolphenol; 2,3-dimethoxyphenol; 2,2-methoxy-bis(4-chloro-phenol); and para-phenylphenol.

The references of record do not suggest treating a body with one or more of the above-mentioned phenols and an inorganic salt at a concentration of at least 2%. The salt treatment method taught by Foster does not destroy prions. Thus, there is no suggestion for use of sodium chloride in a phenol-based disinfectant, such as LpH, as taught by Ernst and Race. Nor is there any suggestion that the salts proposed by Foster would be useful as agents favoring unfolding in Kritzler's system. There is no suggestion in Foster that the prions undergo conformational unfolding in the process.

Accordingly, it is submitted that claim 23, and claim 24 dependent therefrom, distinguish patentably and unobviously over the references of record.

Claim 29 calls for a method of treating a body which is contaminated with infectious prions. The method includes contacting the body with a composition to inactivate prions on the body. The composition includes a phenol, a cosolvent, water, and a surfactant selected from the group consisting of sulphonic acids, sulfonates, and combinations thereof.

In paragraph 0041, Kritzler discloses that certain surfactants tend to bind to proteins and initiate unfolding of their tertiary structure. This paragraph, however, details the understanding about proteins in general and not about prion proteins. There is no suggestion that detergents affect conformational change in prions or have any effect on the infectivity. Note in particular, the Darbord reference, which indicates that detergents are ineffective against prions.

Nor is there any suggestion that they should be used in eombination with phenols.

As the prior art indicates, the behavior of prions is not predictable. Thus, one of ordinary kill in the art would have no expectation of success in combining a surfactant selected from the group consisting of sulphonic acids and sulfonates with a phenol.

Thus, it would not have been obvious, in view of the cited references, to contact a body with a composition which includes a phenol, a cosolvent, water, and a surfactant selected from the group consisting of sulphonic acids, sulfonates, and combinations thereof.

Accordingly, it is submitted that claim 29, and claim 10 dependent therefrom, distinguish over the refcrences of record.

New **claim 30** mcthod of treating a body which is contaminated with infectious prions. The method includes contacting the body with a composition to inactivate prions on the body, the composition comprising *o*-phenylphenol and *o*-benzyl-*p*-chlorophenol, a cosolvent, sodium chloride, water, and a surfactant, the composition effecting a change in the three dimensional structure of thc prion protein and inactivating prions on the body.

Support for claim 30 is to be found in claims 13 and 29 and in the specification at page 12, lines 1-5 and page 19, lines 7-14.

The references of record do not suggcst treating a body with a composition as claimed.

☒ Remaining Claims, as delineated below:

(1) FOR	(2) CLAIMS REMAINING AFTER AMENDMENT LESS HIGHEST NUMBER PREVIOUSLY PAID FOR		(3) NUMBER EXTRA
TOTAL CLAIMS	27	- 26 =	1
INDEPENDENT CLAIMS	6	- 5 =	1

CONCLUSION

For the reasons set forth above, it is submitted that claims 1-18 and 22-30 (all pending claims) distinguish patentably over the references of record and meet all statutory requirements. An early allowance of all claims is requested.

In the event the Examiner considers personal contact advantageous to the disposition of this case, she is requested to telephone the undersigned at (216) 363-9000.

Respectfully submitted,

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